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(54) Title: PROCESS FOR THE PREPARATION OF 4,6-DICHLOROPYRIMIDINE

(57) Abstract

A process for preparing 4,6-dichloropyrimidine comprising treating 4,6-dihydroxypyrimidine with phosgene in the presence of a suitable base and optionally in the presence of a solvent.

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PROCESS FOR THE PREPARATION OF 4,6-DICHLOROPYRIMIDINE

The present invention relates to a process for converting 4,6--dihydroxypyrimidine (1) into 4,6-dichloropyrimidine (2) using phosgene and a suitable base. 4,6-Dichloropyrimidine is useful as a chemical intermediate in the agrochemical industry. It is especially useful in the preparation of ICIA5504.

It is known, for example, that phosphoryl chloride in the presence of dimethylaniline will convert 4,6-dihydroxypyrimidine to 4,6-dichloropyrimidine (Journal Chemical Society (1943) 574-5, and ibid (1951) 2214). The problem with these methods is that, when used on a large scale, a considerable amount of phosphoric acid by-product is produced and this must be disposed of in some way.

The present invention provides a process for preparing 4,6-dichloro-pyrimidine comprising treating 4,6-dihydroxypyrimidine with phosgene in the presence of a suitable base.

4,6-Dihydroxypyrimidine (1) can also exist in the tautomeric forms (A) and (B) and references to 4,6-dihydroxypyrimidine include all its tautomeric forms.

Suitable bases include tertiary amines of formula $R^1R^2R^3N$ (wherein R^1, R^2 and R^3 are, independently, C_{1-10} alkyl, aryl, heteroaryl or aryl(C_{1-4})alkyl) and heterocyclic amines optionally substituted by C_{1-10} alkyl. Examples of tertiary amines are triethylamine, 4-(N,N-dimethylamino)-pyridine, N,N-diisopropylethylamine and especially dimethylaniline. Examples of heterocyclic amines are pyridine, 2-methylpyridine, 4-methylpyridine, imidazole and N-alkyl pyrrolidines (such as N-methylpyrrolidine).

It is preferred that the base:phosgene molar ratio is in the range 1:10 to 10:1, especially in the range 1:1 to 1:4 (such as 2:3 and 2:4.5).

Alkyl groups are straight or branched chain and, unless stated otherwise, preferably contain from 1 to 6, especially from 1 to 4, carbon atoms. Examples are methyl, ethyl, iso-propyl, n-propyl, n-butyl and tert-butyl.

Aryl is preferably phenyl.

Heterocyclic amines are preferably saturated or unsaturated 3-7 membered carbon nitrogen rings. They are, for example, pyridine,

imidazole, pyrrolidine or piperidine.

Heteroaryl is a 3-7 membered carbon nitrogen ring. It is, for example, pyridine, imidazole, pyrazole or pyrrolidine.

It is preferred that the process is carried out in a solvent or mixture of solvents. Chlorinated solvents (such as dichloromethane, 1,1,2,2-tetrachloroethane or chlorobenzene), ethers (such as tetrahydrofuran, glyme, diglyme or triglyme), polar aprotic solvents [such as esters (for example a C_{1-4} alkyl ester, such as methyl formate or iso-propyl formate) or nitriles (for example propionitrile, butyronitrile, benzonitrile or acetonitrile)] are preferred. Mixtures of solvents include, for example, a mixture of acetonitrile and dichloromethane.

The process is preferably carried out in the temperature range -10°C to 130°C, especially 0°C to 120°C, particularly 10°C to 90°C.

In one aspect the present invention provides a process for preparing 4,6-dichloropyrimidine comprising adding phosgene to a mixture of 4,6-dihydroxypyrimidine and a suitable base.

In a further aspect the present invention provides a process for preparing 4,6-dichloropyrimidine comprising adding phosgene to a mixture of 4,6-dihydroxypyrimidine and a suitable base, wherein all the phosgene to be used in the process is added at the beginning of the process.

In another aspect the present invention provides a process for preparing 4,6-dichloropyrimidine comprising adding phosgene to a mixture of 4,6-dihydroxypyrimidine and a suitable base (such as dimethylaniline or diisopropylethylamine) in a chlorinated solvent, wherein the molar ratio of 4,6-dihydroxypyrimidine:suitable base:phosgene is in the range 1:(0.8 to 2.5):(2.5 to 3.6) especially in the range 1:(1.5 to 2.2):(2.9 to 3.3).

In yet another aspect the present invention provides a process for preparing 4,6-dichloropyrimidine comprising adding phosgene to a mixture of 4,6-dihydroxypyrimidine and a suitable base (such as dimethylaniline or diisopropylethylamine) in a nitrile solvent, wherein the molar ratio of 4,6-dihydroxypyrimidine:suitable base:phosgene is in the range 1:(0.1 to 2.4):(4 to 9) especially in the range 1:(0.1 to 2.1):(4.4 to 6.5).

In a further aspect the present invention provides a process for preparing 4,6-dichloropyrimidine the process comprising adding phosgene to a mixture of 4,6-dihydroxypyrimidine and a suitable base (such as dimethylaniline) in a suitable solvent (such as dichloromethane,

acetonitrile or tetrahydrofuran), all the phosgene to be used in the process being added at the beginning of the process, and heating the reaction mixture (preferably for 1 to 30, especially 1 to 6 or 15 to 24 hours). The suitable base can be recovered (in salt form) during the product isolation and can be recycled.

The following Examples illustrate the invention. The apparatus used in the following Examples was dried before use, and reactions were conducted under nitrogen using anhydrous conditions.

EXAMPLE 1

4,6-Dihydroxypyrimidine (0.94g) was suspended in dichloromethane, dimethylaniline (1.12g) added and phosgene (5g) was then condensed into the mixture. The resulting mixture was heated at reflux for 24 hours, then cooled and poured into water. High pressure liquid chromatographic (hplc) analysis of the resulting organic layer showed a 4,6-dihydroxypyrimidine: 4,6-dichloropyrimidine ratio of 39:58.

EXAMPLE 2

4,6-Dihydroxypyrimidine (20.5g) was dispersed with agitation in dichloromethane (400ml). Dimethylaniline (40.4g) was added to the agitated mixture and the system was sealed (except for a vent line to a scrubber). Phosgene gas (56g) was introduced from a cylinder and condensed onto a cold finger and collected in a pressure equalised dropping funnel. Once collected, the phosgene liquid was added to the reaction mixture over 15 minutes. The mixture was heated and agitated at reflux (29°C approximately) for 17 hours after which time the mixture was cooled to room temperature and the excess phosgene removed by sparging with nitrogen.

Water (400ml) was added slowly to the agitated reaction mass with cooling to maintain the temperature at ambient. The organic layer was separated, and the aqueous was then extracted with dichloromethane (2 x 100ml). The combined extracts were dried over anhydrous sodium sulphate and concentrated by rotary evaporation to give 4,6-dichloropyrimidine as an orange crystalline solid (27g), equivalent ot a yield of 80% (hplc analysis).

EXAMPLE 3

4,6-Dihydroxypyrimidine (2.0g) was dispersed with agitation in acetonitrile (40ml), dimethylaniline (2.1g) was added and the mixture was heated to 50°C. Phosgene gas (14.6g) was added to the mixture (by bubbling

it through the mixture) over 1 hour. The mixture was kept at 50°C for 4.5 hours, cooled to room temperature, and the excess phosgene removed by sparging with nitrogen. Analysis (hplc) of the resulting reaction mass showed it to comprise 4,6-dichloropyrimidine (in 81% yield).

EXAMPLE 4

To a mixture of 4,6-dihydroxypyrimidine (5.14g, 1 equivalent) and imidazole (6.19g, 2 equivalents) in acetonitrile (100ml) was added phosgene (28g, 6.2 equivalents). The resulting mixture was stirred for 2½ hours at room temperature and for 1 hour at 50°C. The reaction mixture was purged with nitrogen overnight and then partitioned between water and dichloromethane. The organic layer was separated and the aqueous extracted twice more with dichloromethane. The organic extracts were combined, washed with water (twice), dried over magnesium sulphate and evaporated to dryness to leave 4,6-dichloropyrimidine as a pale yellow solid.

EXAMPLE 5

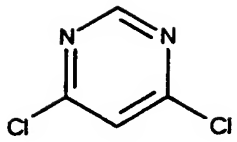
To a stirred mixture of 4,6-dihydroxypyrimidine (5.18g, 1 equivalent) and 4-(N,N-dimethylamino)pyridine (0.55g, 0.1 equivalent) in acetonitrile (100ml) was added phosgene (28g, 19.7ml, 6.2 equivalents) in two aliquots. The resulting mixture was stirred for 10 minutes at room temperature and was then stirred for 4 hours at 55°C. The reaction mixture was purged with air after which water (200ml) was added. The resulting mixture was extracted with dichloromethane (3x100ml). The organic extracts were combined, washed with water (100ml), dried over magnesium sulphate and evaporated to dryness to leave 4,6-dichloropyrimidine (4.63g).

EXAMPLE 6

To a stirred mixture of 4,6-dihydroxypyrimidine (5.18g, 1 equivalent) and N,N-diisopropylethylamine (11.75g, 2 equivalents) in acetonitrile (100ml) was added phosgene (28g, 19.7ml, 6.2 equivalents) in two aliquots. The resulting mixture was stirred for 10 minutes at room temperature and was then stirred for 4 hours at 55°C. The reaction mixture was sparged with air overnight after which water (100ml) was added. The resulting mixture was extracted with dichloromethane (3x100ml). The organic extracts were combined, washed with water (100ml), dried over magnesium sulphate and evaporated to dryness to leave 4,6-dichloropyrimidine (6.35g).

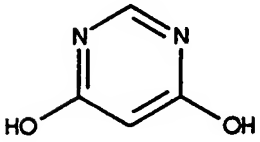
CHEMICAL FORMULAE

(In Description)



(2)

4,6-dichloropyrimidine

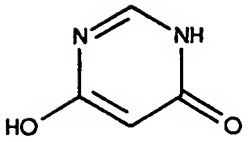


(1)

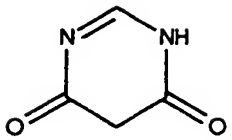
4,6-dihydroxypyrimidine

$COCl_2$ phosgene

$POCl_3$ phosphoryl chloride



(A)



(B)

CLAIMS

1. A process for preparing 4,6-dichloropyrimidine comprising treating 4,6-dihydroxypyrimidine with phosgene in the presence of a suitable base.

2. A process as claimed in claim 1 wherein the base:phosgene molar ratio is in the range 1:10 to 10:1.

3. A process as claimed in claim 1 or 2 wherein the process is carried out in a solvent or mixture of solvents.

4. A process as claimed in claim 1, 2 or 3 wherein the base is a tertiary amine of formula $R^1R^2R^3N$ (wherein R^1, R^2 and R^3 are, independently C_{1-10} alkyl, aryl, heteroaryl or aryl(C_{1-4})alkyl) or a heterocyclic amine optionally substituted by C_{1-10} alkyl.

5. A process as claimed in claim 1, 2, 3 or 4 wherein phosgene is added to a mixture of 4,6-dihydroxypyrimidine and a suitable base.

6. A process as claimed in claim 1, 2, 3, 4 or 5 wherein the process comprises adding phosgene to a mixture of 4,6-dihydroxypyrimidine and a suitable base in a chlorinated solvent, wherein the molar ratio of 4,6-dihydroxypyrimidine:suitable base:phosgene is in the range 1:(0.8 to 2.5):(2.5 to 3.6).

7. A process as claimed in claim 1, 2, 3, 4 or 5 wherein the process comprises adding phosgene to a mixture of 4,6-dihydroxypyrimidine and a suitable base in a nitrile solvent, wherein the molar ratio of 4,6-dihydroxypyrimidine:suitable base:phosgene is in the range 1:(0.1 to 2.4):(4 to 9).

8. A process as claimed in any one of the preceding claims wherein the base is dimethylanilane or diisopropylethylamine.

INTERNATIONAL SEARCH REPORT

Interna l Application No
PCT/GB 95/00676

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FR,A,1 310 810 (BASF) 22 October 1962 see page 8; claims; example 29	1-7
Y	EP,A,0 095 637 (BAYER) 7 December 1983 see page 1 - page 8	1-7
Y	EP,A,0 173 191 (BAYER) 5 March 1986 see page 1 - page 8; claims	1-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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16 May 1995	23. 05. 95

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FR-A-1310810	13-03-63	DE-B-	1164418	
		US-A-	3365452	23-01-68
EP-A-0095637	07-12-83	DE-A-	3220105	01-12-83
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